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The relationship between nutritional status and heart rate variability in elderly patients

Nutrition and heart rate variability

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Abstract
Aim: Malnutrition is a common health problem in elderly patients. Prognostic nutritional index (PNI) and geriatric nutritional risk index (GNRI) are two easily-calculable indexes developed as indicators of nutritional status, showing prognosis relationships with some diseases. We planned a study to define the relationship between PNI, GNRI, which indicates nutritional status and is also a criterion of frailty, and heart rate variability (HRV), which is a cardiovascular risk marker.
Material and Methods: A total of 96 patients over 65 years of age who had no known chronic disease other than controlled hypertension and regulated diabetes and who underwent rhythm holter monitoring were evaluated. Framingham risk scores (FRS), PNI, GNRI of the patients were calculated. HRV parameters were recorded.
Results: The root mean square of successive differences (rMSSD) (p:0.02) and percentage of adjacent RR intervals with a difference of duration >50ms (pNN50) (p:0.035) were significantly lower in the patient group with low PNI. HRV frequency domain parameters, low-frequency/high-frequency (LF/HF) (p:0.048) and total power (TP) (p:0.044) were significantly higher in the patient group with low PNI. There was no significant relationship between GNRI and HRV parameters.
Discussion: PNI is a simple indicator of decreased HRV and increased cardiac risk in elderly patients. PNI is more valuable than GNRI in predicting increased cardiac risk related to HRV in elderly patients. The results of our study support the effect of adequate nutrition on cardiac autonomic modulation in the elderly and confirm that nutrition in this age group is a correctable cardiac risk factor.

Keywords
Elderly patient; Nutritional status; Serum albumin; Heart rate; Rhythm holter

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Introduction

Physiological changes, acute and chronic diseases that occur with aging adversely affect nutrition. In old age, the incidence of chronic diseases and malignancies increases and cognitive abilities decrease. Malnutrition is common as a result of psychological problems and care problems [1]. Knowing how aging and malnutrition affect the cardiovascular system structurally and functionally may provide the opportunity to prevent or reduce the risk of developing cardiovascular disease in elderly patients.

Heart rate variability, defined as cyclic changes in sinus velocity over time, is a method used to evaluate the autonomic function of the heart, providing information about sympathetic-parasympathetic balance. Reduced HRV is evaluated as a determinant of increased risk for cardiovascular disease and mortality [2]. It has been found that low parasympathetic activity is a marker for poor prognosis in patients with acute coronary syndrome without ST elevation [3].

PNI has been associated with different inflammatory processes in several studies. The relation of PNI with acute heart failure, cardiac surgeries, some cancers and survival and mortality has been demonstrated in previous studies [4,5].

The GNRI is a nutritional index developed to provide information about the severity of malnutrition and mortality in hospitalized elderly patients [6]. There are studies showing that it is a prognosis marker in heart failure [7,8].

In our study, elderly patient group without chronic diseases except for controlled hypertension and regulated diabetes mellitus was evaluated. Old age is an important risk factor for cardiac diseases. It is important for preventive medicine to evaluate the cardiac effects of nutrition before chronic diseases develop. We planned a study to evaluate the relationship between PNI and GNRI, which indicates nutritional status, and HRV, which is a cardiac risk marker, in partially healthy patients over 65 years of age.

Material and Methods

All patients over the age of 65 who applied to the cardiology clinic of Gulhane Training and Research Hospital between June 2019 and June 2020 with complaints of palpitations and who underwent rhythm holter monitoring were evaluated. Patients with a diagnosis of coronary artery disease, heart failure, chronic liver, kidney disease and cancer, those taking medications that may affect rhythm, those with acute or chronic infections, those with rheumatological disease, those without serum albumin and lymphocyte data, and those without height and weight data, uncontrolled hypertension and insulin users with complicated diabetes and active smokers, patients with atrial and ventricular arrhythmias were excluded from the study. Ninety-six patients out of 1225 holter records who met the inclusion criteria were included in the study. The study was compliant with the Helsinki Declaration and was approved by the local ethics review committee.

Biochemical analysis and nutritional status evaluation

The initial demographic and clinical variables of the study population were recorded from the data in the hospital database. Serum creatinine, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride and hemoglobin values were recorded at the hospital admission. The FRS of the patients was calculated according to age, gender, total cholesterol level, HDL cholesterol level, and systolic blood pressure. According to the FRS, patients were divided into 3 categories as high, medium and low risk. Patients with a 10-year adverse event risk > 20% were considered high-risk, 10-20% were considered medium-risk, and <10% were considered low risk [9]. Body mass index (BMI) was calculated using the formula: body mass index = body weight / (height) ^{2}.

Prognostic Nutritional Index

PNI was calculated on the basis of admission data as follows: 10 x serum albumin (g/ dl) + 0.005 x total lymphocyte count (per mm3) from the report of Onodera et al. A PNI value ≥ 50 is defined as normal, <50, as mild- moderate malnutrition [5].

Geriatric Nutritional Risk Index

In this study, GNRI was calculated from serum albumin and BMI by examining the data during outpatient clinic examination [6].

Calculation of GNRI

GNRI= 14.89 × serum albumin (g/dL) + 41.7 × BMI/22

When the BMI / 22 of the patient is greater than 1, the BMI / 22 is calculated as 1.

Since the stable elderly patient group was evaluated in our study, the number of patients that could be considered moderate and severe malnutrition was low and the patients were divided into 2 groups with GNRI <100 and ≥ 100.

Holter rhythm analysis

Twenty-four -hour Holter electrocardiography data were evaluated using a 5-lead Holter device (Northeast Monitoring, Inc. DR181 Holter Recorder, 3-channel Holter) to evaluate heart rate variability. HRV parameters were automatically determined with the holter data processing program. HRV time and frequency domain parameters determined by the automatic analysis method were recorded from the existing holter records of all patients [10].

Statistical analysis

Data analyses were performed using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, United States). Whether the distribution of continuous variables was normal or not was determined using the Kolmogorov- Smirnov test. Levene's test was used for the evaluation of homogeneity of variances. Unless specified otherwise, continuous data were described as mean ± SD for normal distributions, and median (minimum statistical analysis differences in normally distributed variables between two independent groups were compared using Student's t- test; the Mann-Whitney U test was applied for comparisons of the not normally distributed data. While the differences in normally distributed variables among more than two independent groups were analyzed using One-Way ANOVA, otherwise, the Kruskal-Wallis test was applied for comparisons of the not normally distributed data. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test, and p- value <0.05 as was accepted as a significant level for all statistical analyzes.

Results

The laboratory data of the patients and analysis results of HRV time and frequency domain parameters are summarized

Table 1. Demographic data, laboratory findings and HRV parameters of the study population

n (96)	$\bar{X}$ ± SD	Median (Minimum-Maximum)
Age (years)	72.05±4.89	71(60-85)
BMI (kg/m²)	26.36±1.80	25.85(23.10-32)
Hemoglobin (g/dl)	13.43±1.26	13.40(10.50-16.80)
Lymphocyte (10⁹/l)	2.07±0.61	2.01(0.60-3.31)
Creatinine (mg/dl)	0.99±0.18	0.98(0.65-1.50)
Albumin (g/dl)	4.05±0.30	4.05(3.30-4.70)
Total cholesterol (mg/dl)	207.31±46.15	211(100-348)
Triglyceride (mg/dl)	152.73±63.03	140(45-437)
LDL (mg/dl)	123.21±38.18	121(46-258)
HDL (mg/dl)	51.96±13.31	50(29-107)
GNRI	102.57±5.71	102(90.83-119.57)
PNI	50.55±4.56	50.25(42.50-59.80)
FRS	13.68±6.89	18.25(1.30-33.20)
SDNN (msn)	134.17±49.31	126.21(54.43-359.63)
SDANN (msn)	105.20±31.85	101.13(37.56-196.02)
SDNNI (msn)	56.62±43.06	45.36(14.03-312.10)
rMSSD (msn)	58.44±75.04	32.52(10.90-448.06)
pNN50 (%)	11.24±17.59	5.22(0.12-88.09)
VLF(ms²)	6168.66±6869.14	4054.5(249-35818)
LF(ms²)	7801.89±10790.57	3442.5(182-58318)
HF(ms²)	5094.03±7081.80	1864.5(67-34190)
LF/HF	1.80±0.47	1.81(0.91-3.40)
TP(ms²)	19477.64±24408.48	9343(13-128322)
Minimum Heart Rate	50.12±6.97	49(33-69)
Maximum Heart Rate	119.73±9.52	118(101-147)
Mean Heart Rate	73.07±6.57	73(55-98)

Continuous variables are expressed as either mean± standard deviation (SD) or the median (min-max). Continuous variables were compared with Student's t- test or Mann- Whitney U test. Statistically significant p-values are in bold. HF: high frequency; LF: low frequency; VLF: very low frequency; pNN50: percentage of adjacent RR intervals with a difference of duration >50 ms; rMSSD: root mean square of differences between adjacent normal RR intervals, expressed in ms; SDNN: standard deviation of all normal RR intervals, expressed in milliseconds; SDANN (standard deviation of the average NN intervals in 5 minute recordings during the study period).

in Table 1. The mean age of the patients was 72.05 ± 4.89 years and 48 (50.0%) were male. The number of patients with hypertension was 64 (66.7%), the number of patients with diabetes was 32 (33.3%). There were 35 (36.5%) patients with GNRI <100 and 48 (50%) patients with PNI <50.

Albumin (p<0.001), triglyceride (p:0.014), hemoglobin (p:0.023), lymphocyte (p<0.001), and GNRI (p<0.001) values were significantly higher in patients with high PNI than in those with low levels. RMSSD (p:0.02) and pNN50 (p:0.035) were significantly lower in the patient group with low PNI. Among the HRV frequency domain parameters, LF / HF (p:0.048) and TP (p:0.044) were significantly higher in the patient group with low PNI. There was no significant relationship between other HRV parameters and PNI (Table 2).

While the mean age of those with high GNRI was statistically significantly lower, albumin (p <0.001), hemoglobin (p<0.001), lymphocyte (p:0.006) and PNI (p<0.001) were statistically significantly higher. There was no significant relationship between GNRI and HRV time and frequency domain parameters. There is a statistically significant difference among FRS risk groups in terms of age, gender, hemoglobin, HDL, PNI, LF, TP, LF / HF ratio. PNI was lowest in patients with high FRS (P:0.045). LF was highest in patients with high FRS (p:0.040). Also, LF/HF ratio was highest in patients with high FRS (p<0.001). TP was lowest in patients with high FRS (p:0.025). Comparison of demographic and clinical data, nutritional indexes and HRV parameters with low-medium-high FRS groups are summarized in Table 3.

Table 2. Clinical, laboratory and HRV parameters of patients according to low and high PNI

	PNI		p
	<50 (n:48)	≥ 50 (n:48)	
Age (years)	72 (65-85)	70 (65-82)	0.206
BMI (kg/m²)	26.50 (24.20-32.00)	25.80 (23.10-29.50)	0.081
Sex			
Female	22 (45.8%)	26 (54.2%)	0.541
Male	26 (54.2%)	22 (45.8%)	
Arterial hypertension	32 (66.7%)	32 (66.7%)	0.999
Diabetes mellitus	17 (35.4%)	15 (31.3%)	0.829
Creatinine (mg/dl)	0.98 (0.70-1.40)	1.01 (0.65-1.50)	0.587
Albumin (g/dl)	3.86 (3.30-4.50)	4.30 (3.90-4.70)	<0.001
Hemoglobin (g/dl)	13.14 ±1.29	13.72 ±1.16	0.023
Lymphocyte (10⁹/l)	1.71 ±0.44	2.43 ±0.54	<0.001
Total cholesterol (mg/dl)	203.21 ±46.07	213.00 ±47.00	0.305
Triglyceride	135.50 (45-250)	157.50 (80-437)	0.014
LDL (mg/dl)	122.06 ±34.70	126.01 ±41.93	0.617
HDL (mg/dl)	50 (29-84)	49 (31-82)	0.172
FRS	14.05 ±7.65	13.32 ±6.12	0.607
GNRI	99.17 (90.83-108.70)	105.73 (99.70-119.57)	<0.001
PNI	46.5 (42.5-50.00)	54 (50.50-59.80)	<0.001
SDNN (msn)	119.82 (54.43-275.20)	131.22 (71.63-249.06)	0.529
SDNNI (msn)	45.30 (14.03-221.70)	45.47 (19.56-225.19)	0.493
SDANN (msn)	104.67 ±30.86	104.89 ±32.36	0.972
RMSSD(msn)	33.01 (10.90-304.22)	52.09 (12.50-312.90)	0.020
PNN50 (%)	5.74 (0.24-88.09)	13.84 (0.12-83.07)	0.035
LF/HF	2.04 ±0.40	1.77 ±0.38	0.048
VLF (ms²)	4678.5 (249 -35818)	2994.00 (429-32727)	0.264
LF (ms²)	4988 (182-58318)	3293.00 (239-39375)	0.078
HF (ms²)	1960.5 (67-34190)	1793.50 (104-24423)	0.583
TP (ms²)	10965 (636-128322)	7289.50 (13-104906)	0.044
Maximum Heart Rate	117.00 (101.10-147.00)	119.00 (106.00-138.00)	0.254
Minimum Heart Rate	51.15 ±7.25	49.10 ±6.60	0.152
Mean Heart Rate	73.54 ±7.07	72.60 ±6.05	0.487

Continuous variables are expressed as either mean± standard deviation (SD) or median (min-max). Continuous variables were compared with Student's t-test or Mann-Whitney U test . Statistically significant p-values are in bold.
HF: high frequency; LF: low frequency; VLF: very low frequency; pNN50: percentage of adjacent RR intervals with a difference of duration >50 ms; rMSSD: root mean square of differences between adjacent normal RR intervals, expressed in ms; SDNN: standard deviation of all normal RR intervals, expressed in milliseconds; SDANN: standard deviation of the average NN intervals in 5 minute recordings during the study period.

Discussion

The present study showed that the HRV time- domain parameters, rMSSD and pNN50 were significantly lower and the HRV frequency domain parameters, LF/HF and TP were significantly higher in the patient group with low PNI. The findings of this study suggest that nutritional status is associated with sympathovagal balance in the elderly.

The autonomic nervous system is involved in nutritional control through the posterolateral hypothalamus and in cardiovascular control with the dorsomedial hypothalamus [11]. Sympathovagal balance disorders and malnutrition in elderly patients are

Table 3. Relationship of low, medium and high FRS with clinical, laboratory and HRV parameters

	Framingham Risk Score			p
	Low (n:34)	Medium (n:41)	High (n:21)	
Age (years)	70.68 ± 3.94	71.46 ± 4.90	75.43 ± 4.91	0.001[b,c]
BMI (kg/m²)	26.43 ± 1.76	26.32 ± 2.04	26.34 ± 1.37	0.965
Sex				
Female	31 (91.2%)	17 (41.5%)	-	<0.001
Male	3 (8.8%)	24 (58.5%)	21 (100.0%)	
Hypertension	24 (70.6%)	22 (53.7%)	18 (85.7%)	0.034
Diabetes mellitus	11 (32.4%)	11 (26.8%)	10 (47.6%)	0.256
Hemoglobin (g/dl)	13.01 ± 0.99	13.72 ± 1.43	13.52 ± 1.14	0.045[a]
Lymphocyte(10^9/l)	2.10 ± 0.59	2.18 ± 0.59	1.79 ± 0.62	0.052
Albumin (g/dl)	4.08 ± 0.30	4.07 ± 0.32	3.95 ± 0.27	0.277
Creatinine (mg/dl)	0.90 (0.70-1.40)	0.97 (0.65-1.50)	1.05 (0.71-1.30)	0.173
Triglyceride (mg/dl)	142 (75-335)	140 (45-437)	162 (81 -303)	0.357
Total cholesterol (mg/dl)	221.29 ± 42.82	205.85 ± 47.16	191.14 ± 47.05	0.059
HDL (mg/dl)	53.5 (39-84)	47 (31-74)	44 (29-75)	<0.001[a,b]
LDL (mg/dl)	132.42 ± 33.69	123.93 ± 41.59	110.67 ± 36.59	0.123
PNI	51.13 ± 4.01	51.18 ± 4.72	48.37 ± 4.62	0.045[b,c]
FRS	6.46 ± 2.35	14.67 ± 2.82	23.45 ± 3.17	<0.001[a,b,c]
GNRI	101.48 (90.83-117.21)	102.75 (93.81-119.57)	99.77 (92.33-105.73)	0.229
SDANN (msn)	99.64 ± 30.21	105.10 ± 30.12	112.46 ± 35.66	0.342
SDNN (msn)	120.48 (68.92-249.06)	130.39 (54.43-275.20)	121.17 (70.51-217.67)	0.647
SDNNI (msn)	40.51 (19.56-225.19)	46.92 (14.03-221.70)	45.65 (25.61-89.26)	0.344
RMSSD (msn)	30.30 (13.44-312.90)	32.56 (10.90-304.22)	33.97 (12.50-116.39)	0.657
PNN50 (%)	4.59 (0.12-88.09)	6.29 (0.24-84.38)	6.70 (0.16-25.27)	0.741
VLF (ms²)	4331 (429-32727)	3994 (249-26835)	2367 (312-35818)	0.556
LF (ms²)	2150.5 (239-30193)	3073 (237-41947)	3953 (182-58318)	0.040 [a,b,c]
HF (ms²)	1556 (104-26008)	2004 (151-23094)	1910 (67-34190)	0.832
LF/HF	1.59 ± 0.38	1.83 ± 033	2.11 ± 0.29	<0.001 [a,b,c]
Total power (ms²)	10650 (771-98401)	8770 (1300-104906)	7620 (959-128322)	0.025 [a,c]
Maximum HR	120.5 (108-147)	118 (104-142)	112 (101-142)	0.088
Minimum HR	51.88 ± 7.57	49.2 ± 6.35	49.10 ± 6.91	0.132
Mean HR	74.38 ± 6.87	73.2 ± 5.79	70.71 ± 7.14	0.130

Continuous variables are expressed as either mean ± standard deviation (SD) or median (min-max value), and categorical variables are expressed as either frequency or percentage. Continuous variables were compared with One Way Anova test or Kruskal-Wallis test, and categorical variables were compared using Pearson's Chi-square test or Fisher's exact test. LSD or Conover-Inman test were performed for the binary comparisons among the groups and the p-value was set at 0.05. Significant differences were found between a: Low vs Medium, b: Low vs High, c: Medium vs High. Statistically significant p-values are in bold.
HF: high frequency; LF: low frequency; VLF: very low frequency; pNN50: percentage of adjacent RR intervals with a difference of duration >50 ms; rMSSD: root mean square of differences between adjacent normal RR intervals, expressed in ms; SDNN: standard deviation of all normal RR intervals, expressed in milliseconds; SDANN: standard deviation of the average NN intervals in 5 minute recordings during the study period.

two important geriatric syndromes. In elderly individuals, malnutrition has many causes, including gastrointestinal motility and changes in hormone secretion that underlie aging anorexia. Hypoalbuminemia is the result of inflammation and inadequate protein and calorie intake in people with chronic disease [12]. While the decrease in albumin in acute events is mostly associated with inflammation, in chronic events it may be due to both inflammation and malnutrition [13].

Similar to other systems in the human body, the nervous system experiences a functional decline with aging. These changes have been described in the somatic and autonomic components of the nervous system. HRV reflects this balance between sympathetic and parasympathetic activity [14]. Pagani et al. suggested that the ratio of LF to HF can be used to measure the changing relationship between sympathetic and parasympathetic nerve activities, that is, sympathovagal balance in both health and disease. Increases in LF/HF reflect the transition to sympathetic dominance and are a tool for assessing cardiovascular autonomic regulation [15].

According to a meta-analysis, anorexia has been reported to play a role in the etiopathogenesis of autonomic dysfunction [16]. There are studies showing increased sympathetic modulation of the autonomic nervous system in malnutrition [17-19]. There are studies supporting that malnutrition in the critical developmental period in children can lead to autonomic imbalance through morphological changes [20,21]. Our study has confirmed that malnutrition in the critical destruction stage can lead to autonomic imbalance in the elderly, as well as during the construction phase in children. As a result, an imbalance in the autonomic nervous system with aging may cause nutritional deficiency, and nutritional deficiency may adversely affect the sympathovagal balance with increased sympathetic activity.

PNI was initially defined as an indicator of immunonutritional status based on serum albumin level and lymphocyte count. In the study evaluating the effect of PNI on in-hospital and long-term mortality in patients with STEMI, patients with

lower PNI values had 7.9 times more rehospitalization and 6.4 times higher mortality compared to patients with higher PNI [22]. Candeloro et al.'s study found that low PNI values were associated with short-term and long-term mortality in elderly patients hospitalized for acute decompensated heart failure [7]. In a meta-analysis examining the prognostic value of the GNRI score in heart failure, it was found that the low GNRI score independently predicted all-cause mortality and major cardiovascular events in elderly patients with heart failure [8].

There are insufficient data in the literature evaluating the relationship between PNI, GNRI and HRV in elderly patients where nutritional status is important. Our study is important in terms of examining the cardiac effects of nutritional status, which is important in terms of prognosis in different diseases in elderly patients and comparing two nutritional and cardiac prognostic markers.

In our retrospective study, it was observed that those with low PNI had significantly lower HRV in the geriatric age group without chronic disease except for controlled hypertension and regulated diabetes. The RMSSD duration and pNN50 value, which were independent of diurnal changes and other effects and reflected parasympathetic tone, were significantly lower in the group with low PNI than the group with high. There was no significant relationship between GNRI and HRV parameters. When patients were grouped according to FRS, a significant difference was found between the low-medium-high risk groups in terms of the LF / HF ratio, which is assumed to be an indicator of sympathovagal balance. In addition, a significant positive correlation was observed between LF, which is an important indicator for evaluating sympathetic activity, and FRS. Thiese are data proving that increased cardiac risk is related to increased sympathetic tone in patients with high-risk scores.

In addition, in patients over 65 years of age, poor protein and malnutrition in the stage before the development of complicated chronic diseases are associated with higher cardiac sympathetic activity, which may be associated with increased cardiovascular morbidity and mortality through HRV time and frequency domain variables. The relationship between late stage chronic diseases and nutritional indexes has been proven in previous studies, and studies evaluating the importance of nutritional indexes in stable elderly patients are insufficient. Therefore, in terms of preventive medicine, the importance of protein-based correct and adequate nutrition should be emphasized in addition to lipid-poor nutrition recommendations for the elderly patient group, even if they do not have a chronic disease.

Limitations

Our study has some limitations. The study has a cross-sectional and retrospective design, so we do not have data showing the prognostic value of PNI in elderly patients. The relationship and prognostic significance between HRV and PNI in stable hypertensive and diabetic elderly patients can be clarified with prospective studies with larger patient populations.

Conclusion

This study showed that PNI was associated with HRV in the stable elderly patient group. Also, it was found that patients with high FRS have lower PNI values. The PNI calculated from serum albumin concentration and total lymphocyte count is a simple and objective indicator of nutrition, and our findings are important in terms of proving the cardiac importance of correct and high-quality nutrition for elderly patients.

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Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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